UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,372	08/29/2003	Enno Adema	03-769	1588

48801 7590 02/05/2008

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 SOUTH WACKER DRIVE
SUITE 3200
CHICAGO, IL 60606

EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

MAIL DATE	DELIVERY MODE
02/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,372	ADEMA, ENNO	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2007 and 13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *3 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/13/07 and the supplemental response of 11/13/07 have been entered.

2. Claim 1 was amended. Claim 12 was canceled. Accordingly, claims 1-11 are pending in the application, with claims 3 and 5 currently withdrawn. Claims 1-2, 4, and 6-11 are subject to examination below.

Manner of Making Amendments under 37 CFR 1.121

3. Applicant's submissions have been entered. However, Applicant is reminded of the proper format for amendments to the claims. It is noted that claims 3 and 5 have been presented with the incorrect status identifiers (see also the Notice of Non-Compliant Amendment mailed 10/3/07). In addition, claim 12 is presented with the status identifier "canceled", yet text for the claim also is also presented with strike-through marks, which is improper as no text should be presented for canceled claims. See MPEP 714.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 4, and 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...") *Regents of the University of California v. Eli Lilly & Co,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims recite a method for detecting antithrombin III (AT) in a sample that main contain an "interfering factor" using three reagents, R1, R2, and R3.

The claimed reagents encompass a genus of molecules not adequately described by the specification. Similarly, the claims invoke a genus of "interfering factors" that are not adequately described.

Regarding the first reagent R1, the claims require that the reagent comprise an "AT binding partner" and must also be able to interact with an interfering factor under certain conditions, but interact with AT in response to addition of a third reagent R3.

The specification discloses thrombin and factor Xa as examples of suitable AT binding partners [0011] (see also dependent claims 2-3). However, the specification does not identify any

shared partial structure shared by the R1 reagents. As such, the genus has not been identified by a precise definition, but only by reference to desired functional characteristics. Further, the specification does not disclose what structures would be responsible for the desired functional characteristics (binding to AT and "interfering factor"). Absent a disclosed correlation between structure and function, one skilled in the art would not envisage possession of the genus of R1 reagents based on the disclosure of the two species thrombin and factor Xa.

Regarding the second reagent R2, Applicant claims any reagent "for a first determination of the free fraction of the AT binding partner". The specification discloses peptidic chromogenic substrates that are acted on by thrombin [0012] as well as antibodies [0009]. However, the specification does not disclose what structural characteristics of these reagents are responsible for their function. Accordingly, the disclosure of a limited number of species fails to adequately identify the claimed genus drawn to all reagents for determining the free fraction of the AT binding partner.

Furthermore, as discussed above the "AT binding partner" is also not adequately described. Therefore, while Applicant has disclosed a limited number of reagents for determining the free fraction of *thrombin,* one skilled in the art would not envisage possession of methods of determining the free fraction of any AT binding partner. Applicant is attempting to describe an unknown by reference to another unknown.

Dependent claim 4 recites a "chromogenic substrate"; however, there is nothing in the claims that would require that the chromogenic substrate be a substrate of thrombin. Given that not all chromogenic substrates would be cleaved by thrombin to produce a color change, one

skilled in the art would not envisage possession of methods in which R2 was any type of chromogenic agent.

Regarding the third reagent R3, which changes the conditions of the reaction mixture such that the AT binding partner interacts with AT, the specification discloses the single example of heparin [0014]. Claim 6 also requires that the third reagent R3 contain an "accelerator" of the interaction between AT and the AT binding partner. The specification does not disclose any partial structure or physical and/or chemical properties shared by the members of the genus of R3 reagents. There is no disclosed correlation between structure and the necessary functions.

Therefore, while methods involving the use of *heparin* are adequately described (as in instant claim 7), one skilled in the art would not know, based on the specification, what other molecules or compounds would possess the necessary functional characteristics of accelerating or changing the reaction conditions as recited. Indeed, while it is known in the art that heparin potentiates the antithrombin activity of AT by enhancing the rate of formation of the thrombin:AT complex, this specific example fails to convey evidence of possession of all reagents that act in a similar manner to enhance the rate of formation of AT with any "AT binding partner".

With respect to claim 10, the recitation of an "additional AT binding partner" as part of the third reagent R3 is also not adequately described for similar reasons as discussed above with respect to the first reagent R1.

Similarly, although the specification discloses *polybrene* as a reagent that is an antagonist for *heparin,* the specification does not disclose sufficient characteristics to identify the genus of *antagonists for accelerator of the interaction between AT and AT binding partner* as in instant

claim 8. One skilled in the art would not know what other reagents besides polybrene might be capable of antagonizing accelerators as required by the claims.

Finally, the claims refer to a sample that may contain an "interfering factor" that interacts with an AT binding partner under certain conditions. However, apart from thrombin inhibitors such as hirudin, the specification does not disclose what other "interfering factors" would be able to bind to AT binding partners under certain conditions and not others.

Absent sufficient recitation of distinguishing identifying characteristics, the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 112

6. Claims 1-2, 4, and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 recites the limitation "the free fraction of the AT binding partner" in line 7. There is insufficient antecedent basis for this limitation in the claim.

8. Step (b) of claim 1 recites the step of adding a second reagent R2 "for a first determination of the free fraction of the binding partner". This language renders the claim indefinite because it may be interpreted as referring simply to the intended use of the second reagent R2 and does not make clear whether a first determination is actually performed in this step or not.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-2, 4, 6-7, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. (US 4,219,497) in view of Furatu (EP 0 041 366), Morris et al. (US 4,314,987), and Akhavan-Tafti et al. (US 6,068,979).

Plattner et al teach a method of measuring total AT-III activity by taking advantage of the fact that AT-Ill inhibits human (z-thrombin and heparin potentiates the activity of AT-Ill, wherein it is possible to delineate the inhibition of thrombin by AT-III from other plasma proteins (i.e. thrombin essentially does not interact with AT but interacts with interfering factor) by measuring a reaction mixture between thrombin and a chromogenic substrate (i.e. adding a second reagent R2; suitable for immunological determination) through measuring total AT-III as an entity (i.e. adding third reagent R3 to change the conditions such that the AT binding partner interacts with AT and conducting a second determination of free fraction of AT binding partner; R3 separate from R1) distinct from the "progressive anti-thrombin activity" measured in the absence of heparin (i.e. first determination of free fraction of AT binding partner), such that the amount of AT-Ill and the amount of color produced from the substrate cleavage by thrombin are inversely proportional, and the level of AT-Ill can therefore be readily determined (i.e. determining the AT content in the sample from the difference between the first and second

determinations of the free fraction of thrombin; kinetic determination). See column 6, line 28 to column 7, line 6.

Thus, the reference teaches determining total AT-III activity (in which case the measurement occurs in the presence of heparin) as well as progressive anti-thrombin activity (in which case the measurement occurs in the absence of heparin). Both of these measurements are performed by detecting thrombin activity on a chromogenic substrate as instantly claimed.

Plattner et al. differs from the claimed invention in that it fails to specifically teach conducting these two measurements in a single reaction mixture. In other words, Plattner et al. teach performing the claimed determination steps *in parallel*, while the instantly claimed invention requires that they be performed *sequentially*, on the same sample or reaction mixture.

However, it was known in the art to subject a single sample to multiple measurements in sequence. For example, Furatu et al. teach subjecting a sample to a plurality of reactions sequentially (see especially pages 1-4). In one embodiment, a reagent solution containing an enzyme is added to a sample solution to cause enzyme reaction, and the result is determined by colorimetric detection (page 3, the first paragraph). Next, a second reagent solution is added to the first reagent solution and a second detection step is performed (page 3, the last paragraph to page 4, first paragraph).

Furatu et al. teach that one advantage in performing a plurality of measurements on a single sample is that only a very small amount of a sample is used, which decreases the sampling number and omits the need for successive sampling operations (page 2).

Morris et al. teach performing a continuous sequence of tests in time on the same blood sample in order to avoid numerous errors that may be introduced by delays in time, differences in blood samples, etc. (column 3, lines 32-53).

Akhavan-Tafti et al. teach that it is frequently desirable to be able to detect and/or quantify more than one analyte at a time in a single test system; savings in time, reagents and materials can thereby be realized and assay protocols can be simplified (column 1, lines 55-63). The solution proposed by Akhavan-Tafti involves sequential detection (see especially the title and abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to detect thrombin activity in the absence and in the presence of heparin as taught by Plattner et al., but to perform these two measurements *sequentially* in the same reaction mixture rather than in parallel. Performing multiple measurements on a single sample was known in the art, as taught for example by Furatu et al., Morris et al., and Akhavan-Tafti et al. Although these references do not relate to determination of AT-III specifically, given that the chemistry of AT-III/thrombin reaction were well established at the time of the invention (as taught for example in Plattner et al.), it would have been further obvious to perform the measurement of "progressive anti-thrombin activity" in the absence of heparin first, and to then add heparin for determination of total AT-III activity (thereby changing the reaction conditions as recited). Put another way, it would have been obvious to use known techniques to improve upon known methods in which multiple measurements are performed, such as those of Plattner et al.

One would be motivated to perform the measurements sequentially on a single sample in order to minimize the amount of sample required, in order to save time, reagents, and materials,

in order to simplify assay protocols, and/or in order to reduce errors due to delays in time and/or differences in blood samples.

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claims 1 and 6-7 above, and further in light of the evidence of Gitel et al. (US 4,883,751).

The references are as discussed above. Plattner et al. teaches measurement in the presence of *heparin* (i.e., reagent R3), but fails to specify whether heparin is an AT binding partner.

Gitel et al. provides evidence that heparin is an AT binding partner (column 1, line 23). Therefore, when performing the method of Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. as discussed above, it would have been obvious to arrive at the claimed invention because heparin (as taught by Plattner et al.) is an AT binding partner (as evidenced by Gitel et al.).

12. Claims 8-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Exner (US 6,051,434).

The Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fail to specifically teach that the first reagent R1 comprises polybrene.

Exner teaches a mixture including polybrene, in order to reverse the effect of any heparin that may be present in test samples. See column 3, lines 34-37. It would have been obvious to one of ordinary skill in the art at the time of the invention to include polybrene, as taught by Exner, in the step of measuring the progressive anti-thrombin activity, as taught by Plattner et al, in order to reverse the effect of any heparin that may be present in test samples. Since the measurement step of Plattner et al requires determining the activity of anti-thrombin in the absence of heparin, the inclusion of polybrene would ensure the success of the assay, thereby providing motivation to combine Plattner et al and Exner references. In addition; one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the polybrene of Exner in the method of Plattner et al. Furatu, Morris et al., and Akhavan-Tafti et al., since Plattner et al teach measurement steps excluding thrombin:AT-III interaction, and the polybrene of Exner is well known in the art as capable of preventing the effect of heparin on inducing thrombin:AT-III complexes.

13. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Nesheim et al (US 5,308,755).

The Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fails to specifically teach an additional AT binding partner.

Nesheim et al teach the addition of purified Factor Xa, in order to perform a competition assay with heparin for antithrombin III to determine the level of heparin activity. See column 2, line 51 to column 3, line 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. with the addition of purified Factor Xa, as taught by Nesheim et al, in order to perform a competition assay with heparin for antithrombin III to determine the level of heparin activity. Determining the level of heparin activity, as taught by Nesheim et al, would indicate the extent of interaction heparin has with the relationship between thrombin and antithrombin III, as taught by Plattner et al, thereby providing the motivation to combine Plattner et al and Nesheim et al references. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the step of Nesheim et al in the method of Plattner et al, since both Plattner et al and Nesheim et al teach homogenous assays that include heparin and antithrombin II1.

Response to Arguments

14. Applicant's arguments filed 11/13/07 with respect to the rejections of claims 1-2, 4, 6-7, and 11 are rejected under § 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. have been fully considered but are not persuasive of error.

Applicant Argues that the Examiner's reasoning for combining the reference teachings is not specific to the particular situation but is rather a wish list for every clinical assay (Reply, page 5, first paragraph).

This is not found persuasive because the analysis of whether the subject matter of a claim is obvious need not seek out precise teachings directed to the specific subject matter of the claim as apparently argued by Applicant. There is no requirement that the prior art contain an express

suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art.

In the instant case, the teachings of Furatu, Morris et al., and Akhavan-Tafti et al. establish that one skilled in the art at the time of the invention would have recognized the value of performing multiple measurements sequentially on a single sample, instead of in parallel on multiple samples.

As such, although the secondary references do not relate specifically to methods of AT III determination, it is maintained that would have been obvious to use known techniques to improve upon known methods in which a sample is subjected to multiple measurements, such as those of Plattner et al.

Applicant has focused on the differences between the references, namely that Furatu, Morris et al., and Akhavan-Tafti et al. teach sequential detection of different analytes, rather than the same analyte as in the instant claims (Reply, pages 5-6). This is not found persuasive because the test for obviousness involves consideration of what the combined teachings, as opposed to the individual teachings, of the references would have suggested to those of ordinary skill in the art. In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991); In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). The inference of obviousness may be drawn from creative steps that a person of ordinary skill in the art would ordinarily employ. KSR Int'l Co. v. Teleflex, Inc., 127 S.Ct. 1727, 1731, 82 USPQ2d 1385, 1396 (2007).

In the instant case, the Examiner maintains that although Furatu, Morris et al., and Akhavan-Tafti et al. apparently relate to multiple measurements of different analytes rather than

the same analyte, one of ordinary skill in the art would have found the teaching of performing multiple *measurements* on a single sample to be particularly pertinent to the method of Plattner et al., in which multiple measurements of thrombin activity were conducted.

Applicant further argues that the references fail to teach changing of the reaction conditions (Reply, page 6, first full paragraph). This is not found persuasive because claim 1 clearly indicates that this step is accomplished by adding the third reagent R3. Since Plattner et al. teach heparin, when performing the method of Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. it would necessarily follow that reaction conditions would change upon heparin addition.

Applicant does not separately argue the limitations of the dependent claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christine Foster
Patent Examiner
Art Unit 1641

LONG V. LE 02/01/08
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600